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Validation of the electronic prescription as a method for measuring treatment adherence in hypertension

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ABSTRACT

Objective: To validate electronic prescriptions (e-prescriptions) as a method for measuring treatment adherence in patients with hypertension.
Methods: This prospective study initially included 120 patients treated for hypertension in primary care centers. Adherence was measured using the gold standard, the medication event monitoring system (MEMS), versus the index test, the e-prescription program, at baseline and at 6, 12, 18 and 24 months. We calculated the adherence rate using the MEMS and the medication possession ratio (MPR) for the e-prescriptions. We considered patients adherent if they had an adherence rate of 80% to 100%. To validate the e-prescription, we obtained measures of diagnostic accuracy, the Kappa concordance index, and the area under the ROC curve (AUC).
Results: We included 102 patients. Overall adherence was 77.4% by MEMS (95%CI: 66.8-88) and 80.4% (95%CI: 70.3-90.5) by MPR. At 24 months, sensitivity was 87% and specificity, 93.7%. The AUC was 0.903 (95%CI: 0.817-0.989).
Conclusion: Measures of treatment adherence were not significantly different between e-prescription and gold standard at most visits, and the e-prescription showed good discriminatory diagnostic capacity.
Practice implications: If patients are included in an e-prescription program for at least 2 years, e-prescription is an inexpensive method to measure adherence in hypertension.

1. Introduction

Control of hypertension, together with control of different vascular risk factors, is essential for preventing cardiovascular disease [1,2], which have a great impact on society in terms of both morbidity and mortality [3,4]. Achieving good control of blood pressure (BP) requires knowing the possible causes associated with poor control. Among the main causes are therapeutic inertia [5,6] and non-adherence to treatment [7]. The World Health Organization (WHO) defines adherence as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [8]. Adherence to medication is a crucial part of patient care and indispensable for reaching clinical goals [9]. There are many reasons why patients do not take their medication properly, such as forgetfulness, changes in dosage, and time periods when they do not experience symptoms. Indeed, sometimes the patient is not even aware of being non-adherent [10]. Accurate estimates of medication adherence will provide better evidence on the consequences, predictors/risk factors, and strategies to improve medication adherence [9].

Diagnosing non-adherence is complex, and there are no completely reliable or universally applicable methods that can be used in daily practice [11]. An ideal medication adherence measure should be low-cost, user-friendly, easy to carry out, highly

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reliable, flexible, and practical [12]. The medication event monitoring system (MEMS) is one of the more reliable methods to measure adherence, but it is expensive to use. Thus, accurate indirect methods to measure adherence are needed.

Electronic prescriptions (e-prescriptions) are emerging as an important strategy to enhance the safety and quality of the prescribing process, for example in the United States [13,14]. This system allows for prescribing the most medically appropriate and cost-effective prescription at the point of care and transmitting the prescription electronically to the patient's preferred pharmacy [15]. At the end of 2010, over 230,000 physicians and other clinicians, or about one-third of practicing physicians, were actively e-prescribing [16]. Prescription refill records and electronic lids on medication containers provide similar estimates of overall adherence [17], and Porterfield et al. [14] has suggested that e-prescribing has the potential to increase patient safety and medication adherence. This measure of adherence assumes that prescription refilling corresponds to medication-taking behaviour, and that patients are taking drugs according to prescription. This low-cost method can identify patients at risk for treatment failure, show medication-refilling patterns and provide third-party verification of data [9].

Since the advent of e-prescribing [16] and, subsequently the use of the XXI Prescription (Receta XXI) program in Andalusia (Spain) [18], health professionals in this context have been able to use this electronic prescribing system as a tool to measure adherence in chronic disease. However, its validity as a method for measuring adherence is unknown.

In the primary care setting, clinician assessments and self-report are still the most commonly used methods to measure adherence [19]. These indirect methods are cheap and easy to administer, but they are also the least reliable, have poor sensitivity and specificity, and can depend on interviewers' communication skills and the questionnaire design [9]. Given these shortcomings, XXI Prescription may be a good alternative for use in medical consultation to rule out therapeutic non-adherence before making treatment decisions. Therefore, the aim of this study was to validate the e-prescription (XXI Prescription) as a method for measuring adherence to antihypertensive therapy in the treatment of mild-to-moderate hypertension in primary care.

2. Methods

This prospective, longitudinal, multicenter health outcomes research study took place in two primary care centers in Andalusia, Spain, and involved 12 primary care physicians (PCP). The study included outpatients who met the following criteria: aged 40 to 80 years; diagnosed with mild to moderate essential hypertension (mean sitting systolic BP/mean sitting diastolic BP, mild: 140–159/90–99 mmHg, moderate: 160–179/100–109 mmHg) according to the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), ESH-ESC 2013 [1]; on antihypertensive therapy; with the diagnosis of hypertension registered in the medical record and incorporated in the e-prescription program at least three months before study baseline; and gave their written consent. Exclusion criteria were: pregnant or breastfeeding; disabling diseases (e.g. dementia, Alzheimer's disease, neurological diseases, terminal cancer, disabling heart disease); inability or unwillingness to give informed consent; participating in other research studies; or living with someone taking the same antihypertensive medications.

The study began in January 2010 and concluded in December 2012. The enrollment period was six months, and mean follow-up was two years. Patients visited the health center five times: at enrollment (baseline) and at 6, 12, 18, and 24 months. At the enrollment visit, each PCP obtained informed consent and took the medical history, recording in a data entry form patients' weight, height, waist circumference and the average of two BP readings taken with sphygmomanometer on the same arm. At this visit each patient was given a medication event monitoring system (MEMS) for each antihypertensive drug prescribed in the XXI e-prescription. The use of the MEMS was explained in accordance with the health center protocol on their use.

Variables were recorded again at each follow-up visit, with patients bringing their medication bottle to all visits for a computer reading. One PCP from each primary health center was designated to conduct follow-up visits in study patients from each center. The investigator downloaded and subsequently analyzed the MEMS reading using a computer program. The number of times the bottle was opened was validated, eliminating any erroneous openings. The drug dispensing records on Diraya, which is the digital medical record used in the Autonomous Community of Andalusia, were noted from the dispensation module in the pharmacy. This module allows pharmacists to retrieve the medication prescribed to the patient and also receive the information regarding the medication actually dispensed. Failure to achieve the therapeutic objectives [1] was reported to the attending physician, and if the physician prescribed a different drug, this was replaced in the MEMS bottle by the patient. At the final visit the MEMS bottles were collected.

Treatment adherence was measured by both the MEMS, as the gold standard [9], and by the e-prescription program (XXI Prescription), as the index test. In order to validate the e-prescription, its data were compared with the pill count using MEMS in a 2×2 table, and indicators of validity were calculated.

The investigator performed data entry, and the following variables were analyzed: age; gender; number of chronic diseases (diabetes, dyslipidemia, obesity, left ventricular hypertrophy, microalbuminuria, retinopathy, coronary heart disease, peripheral vascular disease, stroke, cancer and other); number of drugs taken; cardiovascular risk factors; body mass index (BMI); abdominal waist circumference; mean clinical BP (SBP and DBP) with their SD; and the differences between two consecutive visits and between baseline and study end.

We calculated the adherence rate (AR) using MEMS and the medication possession ratio (MPR) for the e-prescription according to the formulas: AR per MEMS (total number of tablets presumably taken-MEMS openings/total number of tablets that should have been taken according to dosage [days elapsed] x 100) and MPR per e-prescription (total number of tablets presumably taken-purchased from the pharmacy/total number of tablets that should have been taken according to dosage [days elapsed] $\times$ 100). The AR between two consecutive visits was calculated from the MEMS, as well as the cumulative AR at each visit from the start. The final AR was considered to be the cumulative AR at study end or at withdrawal from the study for any reason, provided that a pill count was performed. The MPR was considered in a similar way. The degree of hypertension control was assessed as 'good' when SBP was less than 140 mmHg and DBP was less than 90 mmHg [20].

The primary outcome was the percentage of the patients who adhered to all the doses according to MEMS. This variable was used to classify the patients as adherent ($AR \geq 80\%$) or non-adherent ($AR < 80\%$). The MEMS was also used to determine the percentage of days the user took one tablet daily, the percentage of doses taken in the recommended time frame (7–9 h) and the therapeutic coverage or time during which the patient was pharmacologically covered by an antihypertensive drug, assuming the drug was effective for 24 h. We calculated all the variables overall and compared them between adherent and non-adherent patients.

To validate the e-prescription, we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative

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